Remarks

Applicants have herein canceled claims 1, 11-13, 16, 17, 19, 20, 23, and 30-45 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter encompassed by all canceled claims in one or more divisional or continuation applications. Claims 24-29 and 46-55 will be pending upon entry of the present amendment.

Support for amendments to the specification and claims made herein can be found throughout the specification as filed. Thus, no new matter has been added.

I. Objections to the Specification

The Examiner has objected to the specification pointing out that the specification contains a typographical error an embedded hyperlinks. Applicants have amended the specification herein so as to delete the offending typographical error and embedded hyperlinks. Accordingly, this objection has been obviated and should be withdrawn.

II. Rejections of the Claims Under 35 USC § 112, Second Paragraph

The Examiner has rejected claims 11, 12, 16, 30-35, and 41-45 under 35 USC § 112, second paragraph for alleged indefiniteness.

Among other assertions, the Examiner alleges: that the term "the secreted portion" of claims 30 and 43 is vague and indefinite because "the secreted portion of ATCC Deposit No. 209224 is not defined in the application"; that claims reciting a percentage sequence identity to molecules encoded in ATCC deposits (claims 11 and 41-45) are vague, indefinite and incomplete because "the sequence of the ATCC Deposits are not clear and definitely disclosed"; and that "[c]laims reciting fragments of molecules encoded in ATCC Deposits (claims 11, 31-33, and 35) are vague, indefinite, and incomplete because the sequence of the ATCC Deposits are not clear and are not definitely disclosed" (*See* Paper No. 022004, at page 4).

Applicants respectfully disagree with these aspects of the rejections.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111,

1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. Moreover, the Federal Circuit recently re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,'" Union Oil Co. v. Atlantic Richfield Co., 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000), hereinafter referred to as "Unocal." While the Applicants must "blaze marks on trees," rather than "simply [provide] the public with a forest of trees," Applicants are not required to explicitly describe each of the trees in the forest. *See* Unocal, 208 F.3d at 1000. The Court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. As the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." Unocal, 208 F.3d at 1001 (emphasis added).

Applicants respectfully disagree with the Examiner and submit that one skilled in the art would reasonably conclude that Applicants had possession of the polypeptides corresponding to that which are the full-length, the secreted portion, and fragments or variants of (i.e., having a recited percentage identity to) proteins encoded by the cDNA contained in the ATCC Deposit. Moreover, Applicants submit that one of ordinary skill could readily and routinely identify, determine, and derive these subject polypeptides based on the disclosure of the present application. Nonetheless, solely in the interest of expediting prosecution, Applicants have canceled the rejected claims without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more continuation applications. Accordingly, this rejection has been obviated.

Applicants submit that in view of the claim cancellations made herein, the rejections of claims under 35 USC § 112, second paragraph for indefiniteness have been obviated and respectfully request that these rejections be withdrawn.

III. Rejection of the Claims Under 35 USC §§ 101 and 112, first paragraph-Enablement

Claims 11, 12, 16, and 24-55 are rejected under 35 USC § 101 for allegedly lacking a patentable utility. *See* page 5 of Paper No. 022004. Specifically, the Examiner states,

> [t]here is no specific, substantial, and credible utility disclosed for SEQ ID NO:86 or claimed fragments or variants thereof. The lists on pages 40-42 are no more than vague hoped for uses that those of skill in the art might hunt for in order to use the claimed polypeptides" *See* lines 8-10 of Paper No. 022004.

Applicants respectfully disagree with this rejection.

Preliminarily, Applicants point out that the initial burden is on the Examiner to establish why one of ordinary skill in the art would *reasonably doubt* Applicants' assertions regarding utility and it is only after this initial burden is met that the burden shifts to the Applicants to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. Applicants respectfully submit that the mere conclusory statement that the utilities asserted in specified pages of the specification are "no more than vague hoped for uses that those of skill in the art might hunt for in order to use the claimed polypeptides" does not provide the detailed, well reasoned, and factually supported explanation that is necessary to establish a *prima facie* adequate to challenge the presumptively correct assertions of utility in the disclosure that are at issue. Accordingly, Applicants respectfully submit that the Examiner has not met the necessary burden to establish and maintain a rejection of the claims for lack of utility under 35 USC § 101.

Specifically, Applicants respectfully submit that no evidence or reasoning has been provided that (1) the logic underlying Applicants' assertions of utility is seriously flawed, (2) the facts upon which Applicants base the assertions of utility are inconsistent with the logic underlying the assertions, (3) the statements of asserted utility in the present application would be considered "false" by a person of ordinary skill in the art, or that (4) the statements of asserted utility in the specification are not specific or substantial. Notwithstanding the above discussion, Applicants demonstrate below that the claimed invention is indeed supported by an asserted specific and substantial utility that is credible.

As disclosed in the specification, HKGAJ54 is primarily expressed in umbilical vein and to a lesser extent in endothelial and brain cells (specification at paragraph [145]) and encodes a protein that shares sequence homology with the *Drosophila* peroxidasin protein which is thought

in the art to be associated with extracellular matrix architecture and development (specification at paragraph [143]). The specification teaches that polynucleotides, polypeptides and antibodies corresponding to HKGAJ54 are useful reagents for diagnosing diseases and conditions, such as cancerous and wounded tissue associated with aberrant expression of polypeptides in the tissues or cell types in which they are expressed (specification at paragraph [146]).

Post filing date publications have confirmed the activities of HKGAJ54 as first described in the instant application.[1] As described in Huminiecki *et al.* (Genomics 79(4): 547-552 (2002); submitted herewith as reference C), expression of sequences corresponding to HKGAJ54 (referred to therein as "Magic Roundabout" and "*ROBO4*") is endothelial cell specific, expressed exclusively in sites of active angiogenesis such as tumor vessels in adults, and is upregulated *in vitro* in cells exposed to hypoxia (see, e.g., Huminiecki *et al.* at: abstract; paragraph spanning page 548, columns 1 and 2; page 549, column 1, first paragraph; and page 550, columns 1 and 2).

Moreover, the specification teaches that the compositions of the invention are "useful in modulating the immune response to proliferative and vascular cells and tissues, particularly, those having aberrant phenotypes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues" (specification at paragraph [149]).

Huminiecki *et al.*, report that:

> A search of CGAP SAGE libraries for magic roundabout found it only in endothelial and tumor libraries (Table 2). This is consistent with *in situ* hybridization results in the adult showing that expression was restricted to tumor vessels (colon metastasis to liver, ganglioglioma, bladder an breast carcinoma). Hypoxic induction of magic roundabout (Fig. 2) could explain selective expression on tumor and not normal tissue vasculature. The lack of expression of magic roundabout in adult tissues, except sites of active angiogenesis, points to a developmental role for this gene.
>
> Selective expression of magic roundabout on tumor endothelium combined with the fact that magic roundabout is a transmembrane molecule has implications for the therapeutic targeting of the tumor vasculature.

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[1] Applicants point out that post-filing date scientific papers, such as the paper discussed herein, may be used to corroborate Applicants' asserted utility. Legal precedent for the use of post-filing date references in this manner can be found in In re Brana, where the Federal Circuit stated that:

> The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. In re Marzocchi, 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4. 51 F.3d 1560, 1567, 34 U.S.P.Q.2D (BNA) 1436 (Fed. Cir. 1995).

> Targeting the tumor vasculature is an effective anti-cancer strategy [15], but has proven difficult to enable in human due to lack of suitable targets. Magic roundabout may well be such a target.
> (Huminiecki *et al.*, at page 550, columns 1 and 2)

Applicants submit that, as corroborated by Huminiecki *et al.*, compositions corresponding to HKGAJ54 (e.g., antibodies that bind the claimed polypeptides) are useful, for example in the diagnosis and/or treatment of diseases and conditions, such as cancer that are associated with aberrant expression of HKGAJ54.

Additionally, the specification discloses that "when tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the GAS pathway....activation of the Jaks-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells." (specification at paragraph [143]). Applicants submit that in view of the homology of HKGAJ54 to peroxidasin, a protein involved in matrix architecture, and the disclosure that supernatant of cultured cells expressing HKGAJ54 activates the Jaks-STAT pathway of a T cell line, one of ordinary skill in the art would reasonably believe that altered expression of this protein is reasonably correlated with one or more of the hematological or immune related disorders disclosed in paragraphs 148 and 149 of the specification. Applicants point out that the specification does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. See M.P.E.P. § 2107.02 (I) at 2100-34. All that is required of Applicants is that there be a *reasonable* correlation between the biological activity and the asserted utility (*see* Nelson v. Bowler, 626 F.2d at 857).

According to the Utility Examination Guidelines, the test for specificity is whether an asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, Utility Examination Guidelines. The disclosed utilities for HKGAJ54 polypeptides discussed above are specific, in that not every protein may be used to, for example, to generate antibodies for diagnosing cancer. Consequently, the skilled artisan would most certainly not consider such a use to be a "throw-away utility" such as landfill.

According to the USPTO's published description of a specific asserted utility, as discussed above, the claimed polypeptides are specific because (1) they are specific for the subject matter claimed (e.g., not all polypeptides have uses in the diagnosis of cancer) and (2) the specification discloses a disease or condition which can be diagnosed (e.g., cancer). Applicants' specification certainly does not suggest "diagnosing an unspecified disease."

Moreover, the disclosed utilities for HKGAJ54 polypeptides discussed above are substantial and credible, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, Revised Interim Utility Guidelines Training Materials, page 6. Pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 USC § 101. *See*, Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). It is well-established that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and satisfies the utility requirement. *Id.* Accordingly, the utilities asserted by Applicants are clearly substantial and credible.

Furthermore, with respect to the Examiner's contention, that "[t]he lists on pages 40-42 are no more than vague hoped for uses that those of skill in the art might hunt for in order to use the claimed polypeptides", Applicants disagree that the recited utilities are "no more than vague hoped for uses" and point out that the disclosure of several uses for the claimed invention does not negate the specificity of any one of those uses. Indeed, the M.P.E.P. at § 2107.02 states "[i]t is common and sensible for an applicant to identify several specific utilities for an invention . . .". Further, "[i]f applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established." *Id. See also,* In re Malachowski, 189 U.S.P.Q. 432 (C.C.P.A. 1976); Hoffman v. Klaus, 9 U.S.P.Q.2d 1657 (Bd. Pat. App. & Inter. 1988). Additionally, Applicants respectfully point out that the disclosure of the relationship to a particular human disease is enough to satisfy the utility requirement because utility can exist for therapeutic inventions "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P. § 2107 (III) at 2100-27. "Usefulness in patent law...necessarily includes the expectation of further research and development. The stage at which an invention in this

field becomes useful is well before it is ready to be administered to humans." In re Brana, 51 F.35 1560, 1568 (Fed. Cir. 1995).

In view of the above, Applicants respectfully submit that the presently claimed invention possesses specific, substantial, credible utilities which constitute patentable utilities under 35 USC § 101. Thus, even assuming, *arguendo*, the Examiner had established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by sufficient evidence to lead one skilled in the art to conclude that at least one of the asserted utilities is more likely than not specific, substantial, and credible. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

For the reasons discussed above in response to the rejection under 35 USC § 101, the claimed invention is supported by a specific, substantial, and credible utility. The Examiner "should not impose a 35 USC § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 USC. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. Therefore, since, as discussed above, the claimed invention complies with the utility requirement of 35 USC. § 101, the rejections under 35 USC. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn. Accordingly, Applicants respectfully request that the rejection under 35 USC. § 112, first paragraph, be reconsidered and withdrawn.

IV. Rejection of the Claims 11, 12, and 36-45 Under 35 USC § 112, First Paragraph-Enablement

Claims 11, 12, and 36-45 are rejected under 35 USC §112, first paragraph for allegedly lacking enablement. Specifically, the Examiner states,

> the specification while being enabling for those polypeptides for which a fixed sequence is disclosed, does not reasonably provide enablement for those polypeptides for all of the polypeptides embraced by the claims.
> .....The instant application does not give one of skill in the art enough guidance to make and use polypeptides that are not of a disclosed fixed sequence that has activity. "
> (Paper No. 022004, at page 5).

Applicants respectfully disagree with this rejection.

Nonetheless, solely in the interest of expediting prosecution, Applicants have canceled claims 11, 12, and 36-45 herein without prejudice or disclaimer. Accordingly, this rejection has been obviated and should be withdrawn.

V. Rejection of claim 11 under 35 USC. § 102 (b)

The Examiner has rejected claim 11 under 35 USC. § 102 (b) as allegedly being anticipated by Zuellig et al (Eur. J. Biochem. 204:453 (1992)).

Claim 11 has been canceled herein, thus obviating this rejection. Accordingly, this rejection should be withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks and amendments be entered and made of record in the file history of the instant application. In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

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Respectfully submitted,

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